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EXAMINER	
NICHOLS, CHRISTOPHER J	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 08/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/083,853	SHIGETA ET AL.	
	Examiner	Art Unit	
	Christopher Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-48* is/are pending in the application.

4a) Of the above claim(s) *21-46 and 48* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20 and 47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I (claims 1-20 and 47) drawn to a method of producing a polypeptide, isolated polynucleotide comprising SEQ ID NO: 1, host cells, and gene delivery vehicle comprising same in Paper No. 10 (28 May 2003) is acknowledged.

2. Claims 21-26 and 48 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 10 (28 May 2003).

Status of Application, Amendments, and/or Claims

3. The Preliminary Amendment filed 29 January 2003 (Paper No. 7) has been entered in full. Claims 1, 2, 6, 7, and 8 have been amended.

Specification

4. The disclosure is objected to because of the following informalities: The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (pp. 21 line 20). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Objections

5. Claims **2** and **7** are objected to because of the following informalities: the claims do not end in a period. Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

6. Claims **1-20** and **47** are rejected under 35 U.S.C. 101 because the claimed invention is not supported by a specific, substantial, and credible asserted utility or a well-established utility.

7. The claims are directed to isolated nucleic acid molecule comprising SEQ ID NO: 2. The specification discloses that SEQ ID NO: 2 encodes the polypeptide SEQ ID NO: 1. The specification asserts that the polypeptide encoded by SEQ ID NO: 2 is a novel growth factor that bears structural similarity with vascular endothelial growth factor (VEGF), fallotein, and platelet derived growth factor (PDGF). US 6455283 (24 September 2002) Ferrara *et al.* teaches that VEGF belongs to a large and diverse group which induce the proliferation of endothelial cells and are expressed in a variety of tissues as multiple homodimeric isoforms (Col. 1 lines 23-67). Khachigian and Chesterman (October 1992) "Platelet-Derived Growth Factor and Alternative Splicing: A Review." Pathology **24**(4): 280-290 teaches that PDGF is a potent mitogen and chemotactic agent and is related to VEGF and placenta growth factor (PGF). PDGF is also found in numerous isoforms, each of which has a distinct biological activity and receptor selectivity (pp. 280-281). Hamada *et al.* (26 January 2001) "Molecular Cloning of *SCDGF-B*, a Novel Growth Factor Homology to SCDGF/PDGF-C/fallotein." Biochemical and Biophysical Research Communications **280**(3): 733-737 teaches that fallotein is believed to be a member of the PDGF/VEGF family. It is distinguished from other members of the family by the presence of two domains, a CUB domain and a conserved PDGF/VEGF family domain (pp. 733). The Specification is silent on the matter of whether or not SEQ ID NO: 2 and the polypeptide

encoded by it (SEQ ID NO: 1) contain these identifying domains. The specification does not disclose any data for any activity for the polypeptides encoded by SEQ ID NO: 2. There are no working examples. There are no well-established utilities for newly discovered biological molecules. However, the specification contains several assertions of utilities. Each will be discussed in turn.

a. *The polynucleotide SEQ ID NO: 2 encodes a novel growth factor:* The Applicant's assertion that SEQ ID NO: 2 encodes a growth factor is credible because it shares sequence homology with several growth factors. However, this assertion is not specific, as the art recognizes a large number of growth factors nor is it substantial. Firstly, LaRochelle *et al.* (May 2001) "PDGF-D, a new protease-activated growth factor." Nature Cell Biology **3**(5): 517-521 teaches the functional comparison of four isoforms of PDGF (PDGF-AA, PDGF-BB, p35 PDGF-DD, and p84 PDGF-DD). Each isoform of the PDGF showed a different level of stimulating growth in the NIH 3T3 cells (Figure 2). Therefore, although closely related, PDGF genes can differ in biological activity. Thus is not clear from the specification or the claims to which growth factor is claimed, what tissues are it expressed in, and at what levels. Secondly, the specification's assertion that SEQ ID NO: 2 encodes a novel growth factor is not a substantial assertion of utility, since significant further research would be required of the skilled artisan to determine what SEQ ID NO: 2's properties are.

b. *The polypeptide (SEQ ID NO: 1) encoded by SEQ ID NO: 2 has growth factor activity:* The specification asserts that SEQ ID NO: 2 encodes a polypeptide that is a novel growth factor which based on its structural similarity to prior art of growth factors

that have been characterized. While this assertion is credible it is neither specific nor substantial. It is not specific because this assertion would not have been accepted by one skilled in the art because the art establishes that growth factors, while structurally similar, are functionally diverse. For instance, US 2003/0100502 A1 (29 May 2003) Beals *et al.* teaches a nucleic acid which shares 100% sequence homology with SEQ ID NO: 2 at positions 1-652bp (Col. 22-31). US 2003/0100502 teaches that the sequence encodes a PDGF homolog ([0002]). It is noted that US 2003/0100502 discloses functional data for the punitive PDGF homolog known as LP85 (Figures 1-10). Yet US 2002/0177193 A1 (28 November 2002) Gao *et al.* teaches a sequence with 99.8% homology to SEQ ID NO: 2 at positions 225-652 bp that is disclosed as a VEGF homolog ([0003]). US 2002/0177193 also teaches that the PDGF family has highly divergent sequences ([0003]). US 2002/0177193 also includes functional data for their disclosed novel PDGF family member (Figure 5). Thus it is not clear which member of the PDGF family is claimed, or if it is a member at all, as there is no functional data presented to validate the assertion. In addition, the sequence search yielded two different molecules which share high homology to SEQ ID NO: 2 thus opening to question what isoform has been instantly claimed and hence the assertion is not specific. Further, the assertion that SEQ ID NO: 2 encodes a growth factor is not substantial because the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. In any case, the art clearly shows that structural similarity of different growth factors is not predictive of expression patterns or functional similarity. In addition, Olofsson *et al.* (9 August 1996) "Genomic Organization of the Mouse and

Human Genes for Vascular Endothelial Growth Factor B (VEGF-B) and Characterization of a Second Splice Isoform." The Journal of Biological Chemistry **271**(32): 19310-19317 teaches that the PDGF/VEGF family only shares 20-45% sequence homology, varies due to alternative splicing, and each isoform differs in biological activity and specificity (pp. 19310). Therefore, the specification's assertion that SEQ ID NO: 2 encodes a polypeptide with growth factor activity is not a substantial assertion of utility, since significant further research would be required of the skilled artisan to determine what those activities are due the differences in sequence.

c. *The polynucleotide can be expressed in cell lines:* The specification asserts that the nucleic acid molecule is useful for expression in cell lines. This asserted utility is credible, but is neither substantial nor specific. Since there is no substantial utility for the encoded polypeptide, there is also no substantial utility for the transformed cell lines. It would take significant further research to determine if the transformed cells could be used for particular diseases, since no nexus between a disease state and an alteration in SEQ ID NO: 2 expression levels or form (i.e. mutations) has been disclosed in the specification. Further, since all nucleic acids can be used to transform cell lines, this asserted utility is not specific.

d. *The polynucleotide is useful as probe or primer:* The specification asserts that the isolated nucleic acid molecule is useful as a probe to detect genes encoding SEQ ID NO: 2 or variants thereof, as primers or hybridization probes in screening libraries, microarrays, amplification procedures, FISH, SAGE, in-situ hybridization, nucleotide sequencing, restriction fragment length polymorphism (RFLP), single-strand

conformation polymorphism assay, and allele-specific oligonucleotide hybridization. This asserted utility is credible, but is neither substantial nor specific. Since there is no substantial utility for the encoded polypeptide, there is also no substantial utility for the nucleic acid probes to identify such. It would take significant further research to determine if the polynucleotide could be used as probes for particular diseases, since no nexus between a disease state and an alteration in SEQ ID NO: 2 expression levels or form (i.e. mutations) has been disclosed in the specification. Further, since all nucleic acids can be used as probes or primers, this asserted utility is not specific.

e. *The polynucleotide can be used to make vectors and/or gene delivery vehicles:* Although credible, this asserted utility is not substantial. The instant specification does not disclose any known disease state, toxin, or poison associated with SEQ ID NO: 2 or its activity. Therefore, it is not clear how the skilled artisan would use a vector or gene delivery vehicle for therapeutic, diagnostic, or research uses. Since significant further research would be required to determine how to use the identified vector or gene delivery vehicle, the asserted utility is not substantial. In addition this utility is not specific as any polynucleotide can be used in such a manner.

f. *The polynucleotide can be used to make fusion proteins:* Although credible, this asserted utility is not substantial. The instant specification does not disclose any known disease state, toxin, or poison associated with SEQ ID NO: 2 or its activity. Therefore, it is not clear how the skilled artisan would use a fusion polypeptide for therapeutic, diagnostic, or research uses. Since significant further research would be required to determine how to use the identified fusion polypeptide, the asserted utility is not

substantial. In addition this utility is not specific as any nucleic acid molecule can be used in such a manner.

g. *The polynucleotide is useful for making transgenic animals:* This asserted utility is credible as a polynucleotide can be used to make a transgenic animal. However, no phenotype has been disclosed for transgenic animal made with SEQ ID NO: 2. In the absence of such disclosure, the skilled artisan would have to experiment significantly in order to determine how the transgenic animals could be used. Therefore, the asserted utility is not substantial. Nor is this asserted utility specific as any given polynucleotide can be used to make a transgenic animal.

h. *The nucleic acid molecule is useful for encoding antigenic portions of SEQ ID NO: 1:* This utility is also not substantial, because there is no substantial utility for the full length polypeptide. If substantial further research is required to determine how to use the full-length polypeptide, then substantial further research is also required to determine how to use antibodies generated from antigenic fragments.

i. *The polynucleotide (SEQ ID NO: 2) can be used in assays for drug screening to identify compounds that modulate nucleic acid expression:* While credible, this asserted utility is not substantial. In such assays, compounds are screened for their ability to up-regulate or down-regulate expression of the nucleic acid molecule. Compounds that have one or the other activity are then labeled as potential drugs. However, the instant specification does not disclose any specific disease state wherein there is a change in SEQ ID NO: 2 expression levels or forms (i.e., mutations). For instance, LaRochelle *et al.* (May 2001) "PDGF-D, a new protease-activated growth factor." Nature Cell Biology

3(5): 517-521 teaches the that PDGF-D and PDGF-B differ in their tissue expression distribution and levels (Figure 2). Therefore, it is not clear how the skilled artisan would use a potential drug identified by this method. Since significant further research would be required to determine how to use the identified potential drugs, the asserted utility is not substantial. In addition this utility is not specific as any nucleic acid molecule can be used in such a manner.

j. *The nucleic acid molecule (SEQ ID NO: 2) can be used to make polypeptides for analysis, characterization, or therapeutic uses:* This asserted utility is not substantial nor specific. In recombinantly expressing a polypeptide, the polynucleotide is transfected into a host cell and then the protein is recovered. However, the instant specification does not disclose any known function for the claimed polypeptide or any disease state, toxin, or poison associated with SEQ ID NO: 2. In addition, this utility assertion is not specific as it can be applied to any given polynucleotide. Therefore, it is not clear how the skilled artisan would use a polypeptide manufactured by this method, for analysis, characterization, or therapeutic uses. Since significant further research would be required to determine how to use the identified polynucleotide, the asserted utility is not substantial.

k. *The polynucleotide (SEQ ID NO: 2) has therapeutic uses:* This is a credible but not substantial asserted utility. The instant specification does not disclose any known disease state, toxin, or poison associated with SEQ ID NO: 2. Therefore, it is not clear how the skilled artisan would use the polynucleotides, vectors, or gene delivery vehicles made with SEQ ID NO: 2 for therapeutic uses. Since significant further research would

be required to determine how to use the identified polynucleotide, the asserted utility is not substantial. In addition this utility is not specific as any nucleic acid molecule can be used in such a manner.

l. *The polynucleotide (SEQ ID NO: 2) is useful to make antisense polynucleotides:* Again, although credible, this asserted utility would only be substantial if the encoded polypeptide has a substantial utility. Otherwise, significant further research would be required of the skilled artisan to use the claimed nucleic acid molecules to make antisense polynucleotides, since it is unclear when it would be desirable to use the antisense polynucleotides. In addition this utility is not specific as any nucleic acid molecule can be used to make antisense polynucleotides.

m. *The polynucleotide (SEQ ID NO: 2) is useful to make a kit:* Again, although credible, this asserted utility would only be substantial if the encoded polypeptide has a substantial utility. Otherwise, significant further research would be required of the skilled artisan to use the claimed polynucleotide to make a kit, since it is unclear when it would be desirable to use said kit. In addition this utility is not specific as any polynucleotide can be used to make kit.

n. *The polynucleotide (SEQ ID NO: 2) can be recorded on computer readable media:* This asserted utility is not substantial. The instant specification does not disclose any known disease state, toxin, or poison associated with SEQ ID NO: 2 or its activity. Therefore, it is not clear how the skilled artisan would use the computer readable media as identified by this method, for therapeutic, prognostic, research, or diagnostic uses.

Since significant further research would be required to determine how to use the identified polynucleotide, the asserted utility is not substantial.

8. Therefore, in the absence of a well-established utility, and the absence of a specific, substantial and credible asserted utility, the claimed invention lacks patentable utility under 35 U.S.C. § 101.

9. If Applicant can submit evidence (in the form of a declaration under 37 CFR 1.132 or post-filing date publications) supporting the specification's assertion that SEQ ID NO: 2 encodes a polypeptide which has a specific function similar to a known growth factor, wherein the specific function was predicted by the specification as originally filed, such would be viewed favorably as evidence of patentable utility.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims **1-20** and **47** are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific and substantial asserted

utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

11. Claims **2, 3, 4, 5, 13,** and **14** are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

12. The claims are drawn very broadly to various fragments, derivatives, and variants of SEQ ID NO: 2.

13. The specification teaches SEQ ID NO: 1 and SEQ ID NO: 2 but as discussed above, neither has a credible, specific, and substantial utility.

14. The specification fails to provide any guidance for the successful expression and use of fragments, derivatives, and variants of SEQ ID NO: 2, and since resolution of the various complications in regards to functionality based solely on sequence homology is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state of the art as outlined below, the quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of formulations with growth factors, mutations, variants, isoforms, and activities with SEQ ID NO: 2's derivatives. In the absence of any guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

15. Since the specification as filed does not provide any guidance or examples that would enable a skilled artisan to use the variants of SEQ ID NO: 2. Additionally, a person skilled in the art would recognize that predicting the efficacy of using a polypeptide function based solely on its sequence homology is highly problematic. Thus, although the specification prophetically considers and discloses general methodologies of making the claimed variants, such a disclosure would not be considered enabling since the state of protein biochemistry is highly unpredictable. The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

16. The following references are cited herein to illustrate the state of the art of protein biochemistry.

17. Concerning the breadth of the claims, Bergsten *et al.* (May 2001) "PDGF-D is a specific, protease-activated ligand for PDGF β-receptor." Nature Cell Biology **3**(5): 512-516 teaches that the PDGF/VEGF family is highly diverse in sequence and diverse in function and specificity (pp. 512; Figures 1 and 2). Thus it is not clear from the Specification whether any given fragments or sequence variants would retain or possess any activity.

18. Regarding the nature of the invention, especially the claimed derivatives and fragments of SEQ ID NO: 2, the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is

extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions [see Wells (18 September 1990) "Additivity of Mutational Effects in Proteins." Biochemistry **29**(37): 8509-8517; Ngo *et al.* (2 March 1995) "The Protein Folding Problem and Tertiary Structure Prediction, Chapter 14: Computational Complexity Protein Structure Prediction, and the Levinthal Paradox" pp. 492-495]. However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often

destroy activity. The art recognizes that function cannot be predicted from structure alone [Bork (2000) "Powers and Pitfalls in Sequence Analysis: The 70% Hurdle." Genome Research **10**:398-400; Skolnick and Fetrow (2000) "From gene to protein structure and function: novel applications of computational approaches in the genomic era." Trends in Biotech. **18**(1): 34-39, especially p. 36 at Box 2; Doerks *et al.*, (June 1998) "Protein annotation: detective work for function prediction." Trends in Genetics **14**(6): 248-250; Smith and Zhang (November 1997) "The challenges of genome sequence annotation or 'The devil is in the details'." Nature Biotechnology **15**:1222-1223; Brenner (April 1999) "Errors in genome annotation." Trends in Genetics **15**(4): 132-133; Bork and Bairoch (October 1996) "Go hunting in sequence databases but watch out for the traps." Trends in Genetics **12**(10): 425-427]. Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

19. Claims **1, 15, 17,** and **18** are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

20. The claims are broadly drawn to pharmaceutical compositions and gene delivery vehicles comprising SEQ ID NO: 2. The Specification does not support therapies using SEQ ID NO: 2 or gene therapy using SEQ ID NO: 2. As discussed above, SEQ ID NO: 2 does not have a credible, specific, and substantial utility therefore it is not enabled for therapeutic uses.

21. The specification teaches that SEQ ID NO: 2 encodes SEQ ID NO: 1.

22. The specification fails to provide any guidance for the successful use of SEQ ID NO: 2 in any therapies or diagnosis of any conditions, and since resolution of the various complications in regards to targeting the role a particular gene in an organism is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state of the art as outlined below, the quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of diseases and disorders in which SEQ ID NO: 2 is involved. In the absence of any guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

23. Since the specification as filed does not provide any guidance or examples that would enable a skilled artisan to use the disclosed polynucleotide as a therapeutic in a patient. Additionally, a person skilled in the art would recognize that predicting the efficacy of using a specific polynucleotide *in vivo* without a credible, specific, and substantial utility as highly problematic. Thus, although the specification prophetically considers and discloses general methodologies of using the claimed pharmaceutical compositions of SEQ ID NO: 2 in therapies,

such a disclosure would not be considered enabling since the state of gene therapy is highly unpredictable. The factors listed below have been considered in the analysis of enablement:

(A) **The breadth of the claims;**
(B) **The nature of the invention;**
(C) **The state of the prior art;**
(D) **The level of one of ordinary skill;**
(E) **The level of predictability in the art;**
(F) **The amount of direction provided by the inventor;**
(G) **The existence of working examples; and**
(H) **The quantity of experimentation needed to make or use the invention based on the content of the disclosure.**

24. The following references are cited herein to illustrate the state of the art of gene therapy.

25. On the nature of the invention and the amount of directed provided in the instant Specification, Kaneda (September 2001) "Gene Therapy: A Battle Against Biological Barriers." Current Molecular Medicine **1**(4): 493-499 teaches that gene therapies protocols must overcome biological barriers inherent to the method to first allow the therapeutic nucleic acid to reach its target (Figure 1). The instant Specification does not disclose any specific disorders, disease, conditions, or any specific tissues in which SEQ ID NO: 2 is expressed such that a person of ordinary skill in the art would have sufficient guidance to practice the invention as claimed.

26. On the amount of direction provided and the quantity of experimentation needed, Eck and Wilson (1996) Goodman & Gilman's The Pharmacological Basis of Therapeutics Chapter 5: "Gene-Based Therapy." pp. 77-100 teaches numerous protocols to practice gene therapy (pp. 83-92). Thus it is not clear from the Specification as to which protocol is best suited to carry out the use of SEQ ID NO: 2 as a therapeutic nucleic acid and as noted above, to which disease or

condition, it would be applicable thus presenting the skilled artisan with an undue burden of experimentation and no guidance.

27. On the nature of the invention, Pfeifer and Verma (2001) "Gene Therapy: Promises and Problems" Annu. Rev. Genomics Hum. Genet. **2**: 177-211 teaches several viral vectors for use in gene therapy methods (equivalent to "gene delivery vehicles") (Figure 1). However, the Specification as filed does not provide sufficient guidance as to which vectors are applicable to practice the invention. And as noted above, no conditions in which SEQ ID NO: 2 is involved in the pathology are as of yet disclosed. Therefore the skilled artisan is confronted with undue experimentation to, through trial and error, first determine the condition to treat with SEQ ID NO: 2 and then the manner of delivery.

28. Thus the specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of gene therapy as exemplified in the references herein.

29. Claims **1-20** and **47** are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

30. The claims are drawn to polypeptides having at least 90 nucleotides with a particular disclosed sequence. The claims do not require that the polypeptide possess any particular conserved structure, or other distinguishing feature, such as a specific biological activity. Thus, the claims are drawn to a genus of polypeptides that is defined by sequence identity.

31. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, and any combination thereof. In this case, the only factor present in the claim that is sufficiently disclosed is a partial structure in the form of a recitation of percent identity. The specification does not identify any particular portion of the structure that must be conserved, nor does it provide a disclosure of structure/function correlation. The distinguishing characteristics of the claimed genus are not described. The only adequately described species is a polypeptide comprising SEQ ID NO: 1 and the polynucleotide comprising SEQ ID NO: 2. No active variants are disclosed. Accordingly, the specification does not provide adequate written description of the claimed genus.

32. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required.

See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

33. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

34. Therefore, only isolated polynucleotides comprising the nucleic acid sequence set forth in SEQ ID NO: 2 and isolated polypeptides comprising the amino acid sequence set forth in SEQ ID NO: 1, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision.

35. Claims **13** and **14** are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

36. The term "heterologous" in claim 2 is a relative term which renders the claim indefinite. The term " heterologous" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Neither the specification nor the art defines the term unambiguously. Thus the metes and bounds of the claims cannot be determined.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

37. Claims **2, 3, 4,** and **5** are rejected under 35 U.S.C. 102(e) as being anticipated by US 6432673 B1 (13 August 2002) Gao *et al.* US 6432673 teaches a nucleic acid sequence that shares 100% sequence homology with bp 1-500 and 225-524 of SEQ ID NO: 2 thus meeting the limitations of claims 2, 3, 4, and 5 (Col. 71-107).

Summary

38. Claims 1-20 and 47 are hereby rejected.

39. The following patents, patent application publications and articles were found by the Examiner during the art search and are here made of note:

a. US 2002/0164710 A1 (7 November 2002) Eriksson *et al.* {shares 100% sequence homology with bp 1-500 of SEQ ID NO: 2}

b. US 2003/0073637 A1 (17 April 2003) Uutela *et al.* {shares 100% sequence homology with bp 1-500 of SEQ ID NO: 2}

c. WO 01/25437 A2 (12 April 2001) CURAGEN Corp. {shares 100% sequence homology with bp 1-652 of SEQ ID NO: 2}

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:00AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

CJN
August 7, 2003

Gary L Kunz

GARY KUNZ
SUPERVISORY PATENT EXAMINER
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